Rare inherited kidney diseases: challenges, opportunities, and perspectives

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Abstract: At least 10% of adults and nearly all children who receive renal-replacement therapy have an inherited kidney disease. These patients rarely die when their disease progresses and can remain alive for many years because of advances in organ-replacement therapy. However, these disorders substantially decrease their quality of life and have a large effect on health-care systems. Since the kidneys regulate essential homoeostatic processes, inherited kidney disorders have multisystem complications, which add to the usual challenges for rare disorders. In this review, we discuss the nature of rare inherited kidney diseases, the challenges they pose, and opportunities from technological advances, which are well suited to target the kidney. Mechanistic insights from rare disorders are relevant for common disorders such as hypertension, kidney stones, cardiovascular disease, and progression of chronic kidney disease.

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Abstract: At least 10% of adults and virtually all children progressing to renal replacement therapy suffer from inherited kidney diseases. These patients rarely die when their disease progresses but remain alive for many years, thanks to progress in organ replacement therapy. However, these disorders have a large negative impact on the quality of life of the patients and on health care systems. Since the kidney regulates essential homeostatic processes, inherited kidney disorders have multi-systemic complications which add to the typical challenges of rare disorders. In this review, we will discuss the specific nature of rare inherited kidney diseases, the challenges they are posing to the society, and the opportunities arising from technologic advances, which are particularly well suited to the kidney as a target organ. Mechanistic insights into rare disorders are relevant for common conditions such as hypertension, kidney stones, cardiovascular disease, and progression of chronic kidney disease in general.

Rare Inherited Kidney Diseases: Challenges, Opportunities and Perspectives

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Summary

At least 10% of adults and virtually all children progressing to renal replacement therapy suffer from inherited kidney diseases. These patients rarely die when their disease progresses but remain alive for many years, thanks to progress in organ replacement therapy. However, these disorders have a large negative impact on the quality of life of the patients and on health care systems. Since the kidney regulates essential homeostatic processes, inherited kidney disorders have multi-systemic complications which add to the typical challenges of rare disorders. In this review, we will discuss the specific nature of rare inherited kidney diseases, the challenges they are posing to the society, and the opportunities arising from technologic advances, which are particularly well suited to the kidney as a target organ. Mechanistic insights into rare disorders are relevant for common conditions such as hypertension, kidney stones, cardiovascular disease, and progression of chronic kidney disease in general.

Introduction

The definition of rare diseases varies around the globe: whereas any disease that affects less than 200,000 persons (e.g. less than 1 in 1,250) is considered 'rare' in the USA, the term is reserved for life-threatening or chronically debilitating diseases affecting fewer than 1 in 2,000 people in Europe,[1] less than 1 in 2,500 people in Japan,[2] and less than 1 in 500,000 people in China.[3] Rare diseases, often qualified as "orphan" diseases to stress their severity, lack of resources and knowledge, and specific conditions for developing or making available drugs, represent a group of 6,000 to 8,000 disorders characterised by a broad diversity of clinical and biological manifestations. They are affecting an estimated 30 million patients in Europe.[1] Approximately 80% of rare diseases have an identified genetic origin.[4] The incidence of a given rare disease may vary substantially between regions or ethnic groups. For instance, congenital nephrotic syndrome of the Finnish type occurs more frequently in Finland (with an incidence of 1 in 8,200) than in other parts of the world.

Rare kidney diseases represent a group of at least 150 different disorders with an overall prevalence of about 60-80 cases per 100,000 total population in Europe and the US.[5-7] At least 10% of adults and virtually all children progressing to renal replacement therapy suffer from inherited kidney diseases, which represent the fifth most common cause of ESRD after diabetes, hypertension, glomerulonephritis, and pyelonephritis, respectively. In contrast to many other rare diseases, patients with inherited kidney disorders rarely die when their disease progresses but - thanks to progress in renal replacement therapy - may remain alive for many years. This apparent advantage is counterbalanced by severely compromised health with poor quality of life of the patients and their families. This is exemplified by children born with severe congenital nephropathies, who nowadays can be dialyzed from neonatal age onwards and thus face many decades of life with end-stage renal disease (ESRD) with a high likelihood of altered physical, cognitive and psychosocial development. Since the kidney regulates essential homeostatic processes, inherited kidney disorders have multi-systemic complications which add to the typical challenges of rare disorders, i.e. highly variable phenotypes, fragmented clinical and biological data collections, lack of standardization of diagnostic procedures and, consecutively, limited knowledge of disease mechanism(s) and natural history.[8]

In this review, we will first discuss the epidemiology, variety and specific nature of *rare inherited kidney diseases of genetic origin* (rare cancers and infections will not be addressed here) and the challenges they are posing to the society at large. We will next address the opportunities that arise from recent technologic advances and high-throughput screening approaches, which are particularly well suited to the kidney as a target organ. We will highlight the link between these technologies and innovative clinical research programs in rare renal diseases and initiatives funded by the European Union

and professional societies, and encouraged by patient organizations and support groups. We will illustrate how these collaborative studies may impact on the clinical management of rare kidney diseases and beyond - as their understanding provides key insights into other rare and common disorders such as hypertension, kidney stones, cardiovascular disease, effect of gender and ageing, and progression of chronic kidney disease.

1. Rare inherited kidney diseases: why they are different

The kidney is characterized by a complex structural organization involving a variety of specialized cell types performing biological functions that are essential for homeostasis. Each kidney contains approximately one million functional units, the nephrons, which include a filtrating body, the glomerulus, followed by a tubular structure made of specific segments. These tubules converge into collecting ducts, which open into the renal pelvis. The physiology principles that sustain the central role played by the kidney have been recently reviewed.[9] The kidneys are exposed to and influence the *milieu intérieur* unlike any other organ, regulating NaCl, potassium, phosphorus, calcium, magnesium and water balance, acid-base homeostasis, oxygen sensing and tissue oxygen supply, hormone and vitamin metabolism, as well as innate and adaptive immunity. The renal tissue also plays an important role in metabolic clearance and secretion of metabolic waste and drug metabolites. These highly regulated functions sustain large quantitative effects and make the body composition very sensitive to changes in kidney function. Primary kidney disorders can thus show a large variety of manifestations and have a significant impact on blood pressure, plasma composition, electrolyte and acid-base homeostasis, cardiac excitability, growth dynamics and puberty, and central nervous/cognitive functions. It is also increasingly recognized that various aspects of renal function may be affected in numerous extra-renal rare disorders or polymalformative syndromes (e.g. cystic fibrosis, Charcot-Marie-Tooth, Donnai-Barrow syndrome).[10-12] The high metabolic demand of the tubular cells (in particular, those lining the proximal tubules) explain why the kidney is frequently involved in mitochondrial cytopathies.[13]

Genetics emerged in nephrology in the 1980s, when development of linkage analysis and positional cloning allowed to map the gene location of the most common form of polycystic kidney disease (ADPKD, in 1985),[14] and identify the first mutation responsible for a monogenic kidney disorder (Alport syndrome, in 1990).[15] This was followed (**Table 1**) by identification of genes involved in a series of classic tubular and glomerular disorders such as nephrogenic diabetes insipidus,[16] Liddle syndrome,[17] Dent disease,[18] Bartter and Gitelman syndromes,[19,20] renal Fanconi syndrome due to nephropathic cystinosis,[21] and steroid-resistant nephrotic syndrome.[22] The identification of the molecular basis of

these disorders was critical to define essential mechanisms that had been predicted by earlier physiological and pharmacological approaches.

With the generalization of high-throughput and next-generation sequencing technologies, an increasing number of clinically-defined renal disorders have been found to have a genetic basis. As of today, the genetic basis of more than 160 rare kidney diseases has been defined (**Table 2**). These disorders are caused by mutations in a large variety of genes coding for proteins sustaining the development and complex functions of the kidney. These proteins include receptors, channels, exchangers, co-transporters, enzymes, transcription factors and structural components that may also play a role in extra-renal organs (bone, eye, brain, ...). A functional classification of rare inherited disorders primarily affecting the glomerulus and the tubular segments is given in **Figure 1**. Standardized analyses based on urine samples are helpful in determining the origin of these disorders.

Apart from the increasing number of monogenic diseases linked to clinically defined entities, the genetics of kidney diseases is also characterized by the cohabitation of single-gene and polygenic disorders. The combination of variants in the same genes or in genes involved in common pathways may cause a spectrum of effect sizes that cannot be explained by conventional genotype-phenotype correlations.[9,23] Furthermore, identification of rare, recessively inherited kidney disorders combined with robust phenotype analysis has substantiated the biological impact of carrier states. A case in point is Gitelman syndrome, caused by loss-of-function mutations in *SLC12A3*, encoding the thiazide-sensitive sodium-chloride cotransporter NCC in the distal convoluted tubule. While the prevalence of Gitelman syndrome is ~20 per million, 1% of the general population are heterozygous carriers of *SLC12A3* mutations. The carrier state for rare inactivating mutations in *SLC12A3* and other genes involved in NaCl transport is associated with lower blood pressure and a reduced risk of hypertension,[24] illustrating the relevance of genes involved in rare kidney disorders for more common disorders such as hypertension, kidney stones, and progression of CKD.

2. Specific challenges

2.1. Unknown genetic cause

Despite considerable progress in understanding the genetic and molecular causes of rare kidney diseases, the majority of nephropathies with a genetic etiology still awaits identification. For instance, abnormalities in approximately 20 genes have been identified as monogenic causes of glomerulopathies, around 40 genes have been associated with specific tubulopathies, and 7 genes with atypical hemolytic

uremic syndrome (aHUS). These explain only 30-40% of familial steroid resistant nephrotic syndrome (SRNS), 40-50% of congenital tubulopathy, and 50-60% of aHUS cases. The actual rates of patients in whom a genetic diagnosis is ascertained in clinical practice are probably much lower since genetic screening is often not or incompletely performed. This is mainly due to the high cost and long turnaround times of conventional genetic screening, the common preconception that establishing a genetic diagnosis will not impact clinical management, and significant differences in terms of accessibility to genetic testing among countries in Europe.[25]

2.2. Limited biomarkers

Apart from the current limitations of genetic diagnostics, there is a lack of non-invasive diagnostic tools and prognostic biomarkers in rare kidney disease. Despite intense research efforts into renal biomarkers, the assessment of kidney disease activity and progression risk is still mainly based upon crude markers such as serum creatinine and global proteinuria. Autoantibodies represent diagnostic markers for certain autoimmune nephropathies such as membranous nephropathy, aHUS and membranoproliferative glomerulonephritis (MPGN), but a major fraction of cases is still unexplained and the predictive value of autoantibodies is limited. The descriptive assessment of kidney biopsy specimens by light and electron microscopy, supplemented by a small set of immunological marker proteins, is still considered the diagnostic gold standard.[26]

2.3. Disease heterogeneity

An increasing number of rare kidney diseases hitherto considered single entities are found to be etiologically heterogeneous. Different genetic and non-genetic abnormalities may affect the same biological pathways and give rise to similar clinical, biochemical and histopathological features. The limited prognostic value of traditional diagnostic nomenclatures is largely explained by their inability to differentiate underlying disease mechanisms. E.g., MPGN can be caused by glomerular deposition of circulating immunoglobulins or immune complexes, by mutations in complement proteins regulating the C3 convertase, and by acquired autoantibodies directed against these proteins or C3 itself. Another example of similar heterogeneity is the renal Fanconi syndrome, defined as a generalized dysfunction of the proximal tubule.[27] Since the conventional histopathological classification does not adequately account for these different etiologies, disease prognosis and responses to specific therapeutic approaches are poorly predicted by traditional disease categories. Novel disease ontologies based on genetic and molecular pathophysiology are only beginning to emerge and will require careful prognostic validation by correlating molecular phenotypes with treatment responses and long-term outcomes.

Considerable phenotypic variability is frequently observed among patients with monogenic

kidney disorders. These phenotypic differences can be the consequence of genetic (locus) heterogeneity, as been found for instance in Bartter syndrome (**Table 2**) in which the severe antenatal form of the disease is specifically associated with mutations in *SLC12A2* or *KCNJ1*, whereas the classical, milder form is caused by mutations in *CLCNKB*.[28] In addition, the position or nature of mutation(s) within a specific disease gene may influence phenotype; e.g. two truncating mutations in *PKHD1* always cause a lethal form of autosomal recessive polycystic kidney disease (ARPKD), whereas the presence of at least one missense mutation can be compatible with life.[29] For the majority of rare inherited kidney diseases, however, such genotype-phenotype correlations are absent due to their low incidence and the difficulty of collecting sufficiently large populations.

Not all clinical variability is imposed by locus or allelic heterogeneity. Indeed, within families affected by the exact same mutation clinical expression may vary considerably, suggesting effects of modifier genes, epigenetic or other modifying factors. Gender may modify the phenotype as has been shown in Gitelman syndrome.[30] Oligogenic modifier effects are suggested to play a role in genetic ciliary diseases, such as nephronophthisis; in patients with homozygous *NPHP1* deletions, the presence of an additional heterozygous *NPHP6* or *NPHP8* mutation might cause additional eye or cerebellar involvement.[31,32] With the exception of these few examples, the search for genetic and epigenetic modifiers in rare inherited kidney diseases has been disappointing to date.

2.4. Model organisms

Knockout and transgenic mouse models are highly informative for *in vivo* demonstration of the effects of genetic variation on renal phenotypes.[33] However, mouse models have multiple limitations including strain effects, adaptation, and differences from humans regarding development, growth, physiology, metabolism and adaptation to CKD.[34,35] Furthermore, the long generation times of mouse models limit their use for rapid phenotyping of multiple candidate renal disease genes in the era of next generation sequencing.[36] Because of these limitations, we are far from having ideal mouse models for most of the inherited kidney disorders, and using the currently available rodent models for developing and testing potential new drugs for human disease is often challenging.

3. Opportunities

3.1. Omics technologies

Recent progress in -Omics technologies has opened an unprecedented window of opportunity in rare renal disease research. Kidney diseases appear particularly suited to high-throughput approaches due to the opportunity to examine molecular events in the diseased organ (**Figure 2**). *Kidney biopsy*

provides the opportunity to study intrarenal biological processes *ex vivo* using transcriptomic and proteomic approaches. Tissue microdissection allows compartment-specific array and sequencing based profiling of mRNA transcripts as well as of non-coding regulatory RNA species. The European Renal cDNA Bank project (ERCB) has worked out compartment-specific gene expression profiles in a large number of microdissected kidney specimens from patients with various renal disorders as well as healthy subjects, which are available as a reference database.[37] Furthermore, *urine* is a readily available non-invasive bioresource to study biochemical traits and molecular readouts directly derived from the organ of interest. *Amniotic fluid*, which reflects at least in part renal function of the foetus, is available prenatally for studies in the context of renal development or transport defects.[38] *Exosome isolation* from urine and amniotic fluid allows to study biomaterials containing membrane and cytoplasmatic proteins, mNRAs, and miRNAs that derive from every epithelial cell type facing the urinary space. Exosome analysis may be particularly useful for disease processes involving the renal tubule, such as lysosomal storage diseases and transporter mutations.[39]

The possibility to apply -omics approaches to such samples should facilitate the identification of molecular signatures and prognostic biomarkers, as suggested by recent studies in more common kidney disorders. Studies of the urine peptidome have identified molecular signatures or individual biomarkers for diabetic nephropathy,[40] allograft rejection,[41] and vesicoureteric reflux.[42] Specific alterations of urinary miRNA expression have been detected in lupus nephritis and allograft rejection,[43,44] and individual miRNAs in urinary exosomes have been associated with renal disease activity.[45] With a rapidly growing number of miRNAs being identified to be involved in disease-associated dysregulation of renal cell types,[46] urinary exosome miRNA analysis may have significant clinical diagnostic potential.

The study of the urine metabolome by NMR spectroscopy and mass spectrometry is another powerful emerging technology to generate molecular 'fingerprints' of diagnostic or prognostic value.[47] Initial applications of urine metabolomics in rare kidney disease demonstrated reliable differentiation of three different genetic forms of renal Fanconi syndrome.[48]

3.2. Next generation sequencing

The perhaps most striking advances are currently being made in the field of molecular genetics. Next generation sequencing (NGS) techniques hold great promise for improving the diagnostic efficiency of rare genetic renal diseases.[49-51] NGS allows simultaneous investigation of all disease genes relevant in the context of a given phenotype, at much reduced cost and turn-around times. Successful application of NGS in diagnostic mutation screening, using disease-specific multi-gene panels, has already been shown for several rare genetic renal disorders with locus heterogeneity, such as Alport syndrome, steroid-

resistant nephrotic syndrome, and nephronophthisis.[52-54] Beyond the disease-specific NGS panels, exome sequencing and potentially even whole genome sequencing will soon become part of routine molecular diagnostics and are expected to further improve the diagnostic yield.

While recent technological progress summarized above has created opportunities to generate unprecedented amounts of genetic and molecular information, the sheer data abundance poses an important new challenge in rare kidney disease research. Bioinformatic capacities and analysis tools need to be developed, and the functional characterization of candidate disease genes and of the pathogenicity of individual mutations requires efficient model systems.

3.3. Model organisms

Despite their limitations, mice continue to represent the major model organism for rare kidney disorders. This has been facilitated by development of cell and time-specific gene-targeting tools and RNA-based technologies to manipulate gene function *in vivo*, and by international consortia for targeted embryonic stem cell clones and large scale N-ethyl-N-nitrosourea (ENU) or gene trapping mutagenesis programs.[33] In parallel, the precision and number of phenotypic traits that can be tested has dramatically increased,[35,55,56] and coordinated mouse phenome projects have been implemented.[57] Recent advances in rat genetics and genome editing, combined with the excellent phenotypic analyses available in over 500 inbred rat strains pave the way for using the rat as an alternative model organism for human diseases.[58-60]

In contrast to mice, simple model organisms provide opportunities for higher-throughput gene manipulation and phenotype quantification. Over the last decade, the zebrafish (*Danio rerio*) has emerged as an applicable system for the study of kidney diseases and renal regeneration, based on conserved genomic organization and nephron structure and cell types.[61] While Zebrafish larvae are ideally suited for analysis of genes involved in kidney developmental disorders and ciliopathies,[62] their use has recently been extended to glomerular disorders,[63,64] and tubulopathies.[65] The *Xenopus* pronephros has also been validated as a model of nephron segmentation, with conservation of genes underlying rare kidney disorders.[66]

Recent studies have shown that the fly (*Drosophila melanogaster*) nephrocyte combines filtration with protein reabsorption and can serve as a simplified model for both the podocytes and the cells lining the renal proximal tubule. For instance, the specialized filtration diaphragm of the nephrocyte is lost in flies lacking the nephrin orthologue, corresponding to the functional loss of nephrin (encoded by *NPHS1*) in human congenital nephrotic syndrome of the Finnish type.[67] Furthermore, the Drosophila orthologs of mammalian cubilin and amnionless (AMN), two major receptors for protein reabsorption in the proximal tubule, function for protein uptake and maintenance of nephrocyte ultrastructure.[68]

Although the nematode model *C. elegans* does not possess an excretory system comparable with the mammalian kidney, conserved kidney disease genes play a role in this organism, including proteins involved in the primary cilium, kidney filtration barrier or vasopressin response.[69,70]

3.4. EU programs, cohorts, biorepositories

A major obstacle to rare disease research is the fragmentation of patient-related information. To overcome this issue, the European Union is supporting the development of disease specific information networks, registries, databases and biorepositories (**Table 3**). Transnational registries are crucial to achieve sufficient sample sizes for epidemiological and clinical research. The European Platform for Rare Disease Registries (EPIRARE) analyzes existing rare disease registries in Europe and provides tools to develop a legal basis and define minimal common data elements and quality standards to allow information exchange between individual registries. The PARENT project will provide researchers with guidelines and tools to support setting-up, management and governance of interoperable patient registries. With even greater ambition, the RD-CONNECT platform was recently launched to integrate European rare disease research projects devoted to NGS and high-throughput approaches. RD-CONNECT is closely linked to the International Rare Diseases Research Consortium (IRDiRC) which was launched in April 2011 to achieve two main objectives: to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases by the year 2020. One of the first clinical research projects partnering with RD-CONNECT is EURenOmics, a consortium for -Omics research in rare kidney diseases. EURenOmics integrates registries and biobanks with detailed phenotype information and biomaterials from more than 13,000 patients to identify new genes, molecular signatures and biomarkers and work towards innovative therapies in patients with rare glomerulopathies, tubulopathies, complement disorders and renal malformations.

Professional and scientific societies are also increasingly involved in fostering rare kidney disease research. ERA-EDTA, the European association of nephrologists has implemented a working group on inherited kidney diseases (WGIKD) to encourage research, to promote improved and affordable care, and to facilitate the dissemination of knowledge to health care providers, patients and their families.[71]

At the local institution level, integrated centers of competence are being established throughout Europe to comply with the EU Commission's request for National Action plans for rare diseases. These will improve high-level health care access and, by the implementation of dedicated transition clinics, facilitate the move of patients with complex, life-long diseases from pediatric to adult care.[72]

3.5. Non-rare inherited kidney disorders

Rare kidney diseases cohabit with ADPKD, one of the most common inherited disorder with a prevalence of 1:1,000 (an estimated 750,000 patients in Europe). Due to the autosomal dominant transmission and slow progression of disease, ADPKD patients represent a very significant pressure group among the much smaller cohorts of patients affected by other inherited kidney diseases. The significant prevalence of ADPKD has impacted on the structure of research funding and drug development and, increasingly, on the structure and clustering of patient organizations. Potential treatments of ADPKD have now been tested in sufficiently powered randomized clinical trials.[73]

3.6. Opportunities for common diseases

The study of rare kidney diseases may provide important insights relevant to more common diseases. A recent example is provided by the *UMOD* gene, whose dominantly inherited mutations cause familial juvenile hyperuricemic nephropathy.[74] Genome-wide association studies (GWAS) subsequently showed that common variants in the *UMOD* promoter are strongly associated with the risk of chronic kidney disease and hypertension in the general population.[75] Further studies revealed that these risk variants increase the transcriptional activity of *UMOD*, and that the *UMOD* gene product uromodulin interacts with the tubular cotransporter NKCC2 to cause salt sensitivity and hypertension.[76] The elucidation of this fundamental molecular mechanism was facilitated by the previous functional characterization of NKCC2 as part of the exploration of Bartter's syndrome.[20] Likewise, variants in the genes encoding the megalin (*LRP2*) and cubilin (*CUBN*) receptors or their regulators (*DAB2*), which are essential for the tubular reuptake of ultrafiltered proteins and defective in some rare diseases, have been identified by GWAS to impact on renal function and the risk of CKD.[77,78] Conversely, GWAS performed to identify common genetic variants predisposing to specific phenotypes may incidentally point to candidate genes for rare genetic diseases. For example, the identification of *CNNM2* as the causative gene for a rare genetic form of severe renal magnesium wasting was based, among others, on a GWAS showing an association between common variants in *CNNM2* and serum Mg^{2+} concentrations.[79]

4. Perspectives

4.1.Diagnostics

The rapidly growing use of NGS for clinical diagnostic purposes is expected to increase diagnostic efficiency in rare monogenic renal diseases. Consequently, accurate genetic counseling as well as possibilities for carrier testing will become available for a growing number of families and allow early

prenatal or preimplantation diagnostic tests to be performed in severe cases. In some rare renal diseases a definite genetic diagnosis may also have important prognostic value. For instance, the efficacy of plasmapheresis and outcome of renal transplantation in aHUS is correlated with the type of complement aberration. Patients with mutations in complement genes encoding circulating proteins (*CFH, CFI*) have a worse outcome than patients with mutations in *MCP*, encoding a cell-associated protein.[80] Likewise, in children with steroid resistant nephrotic syndrome genetic testing helps predicting the response to immunosuppressive therapies and the risk of post-transplant disease recurrence.[81]

4.2. Treatment

The elucidation of disease mechanisms has promoted efficient therapeutic approaches for some rare kidney diseases (**Table 2**). In others, molecular therapies may be closer than anticipated (**Figure 3**).

Cystinosis is a lysosomal storage disease caused by mutations in the *CTNS* gene resulting in intralysosomal accumulation of cystine crystals causing damage in multiple organs including the kidney.[21] The oral administration of cysteamine, which reverses the intralyosomal accumulation of cystine, has been central to the treatment of cystinosis since the 1980's (**Figure 3**). When started early in life, long-term cysteamine therapy significantly delays progression to end-stage renal disease, hypothyroidism, diabetes, and neuromuscular disorders.[82] However, cysteamine does not replace cystinosin, does not prevent the proximal tubulopathy associated with the disease, and is a bothersome life-long treatment with significant side effects. Recent reports of syngeneic bone marrow cell (BMC) and haematopoietic stem cell (HSC) gene therapy as a successful treatment in a mouse model of cystinosis with reduction of cystine content and attenuation of the kidney injury, raise hope that BMC or HSC transplantation may become a potential treatment for cystinosis and other renal tubular disorders.[83]

The elucidation of molecular disease mechanisms may create further opportunities to utilize drugs developed for other purposes in corresponding renal conditions. For instance, proteinuria recurs after kidney transplantation in some patients with focal-segmental glomerulosclerosis (FSGS), frequently leading to graft loss.[84] In some of these cases, proteinuria is linked to a dysfunction of glomerular podocytes which involves upregulation of B7-1, a costimulatory molecule normally expressed in T-lymphocytes, with consequent impairment of the foot process anchoring ß1-integrin proteins.[85] The B7-1 inhibitor Abatacept, approved for the treatment of rheumatoid arthritis, has recently been shown to induce remission of proteinuria in both post-transplant and primary FSGS.[86] Other rare glomerulopathies also involving the inactivation of podocyte integrins might also benefit from this new indication for a drug designed to treat theumatological diseases.

Monoclonal antibodies have recently demonstrated remarkable efficacy in several (ultra)rare renal disease groups. Thanks to their highly specific mechanisms of action, these compounds are ideally suited for targeted therapeutic approaches with minimal side effects.

Rituximab, a B-lymphocyte depleting monoclonal antibody originally developed for the treatment of B-cell lymphoma, has become a useful, albeit still off-label, therapy for rare immunological conditions such as systemic lupus erythematosus,[87] autoimmune vasculitis,[88] and primary glomerulonephritis refractory to standard treatment.[89,90] The use of rituximab promises to improve disease control and minimize exposure to conventional, more toxic immunosuppressive drugs.

Eculizumab is a highly potent inhibitor of the terminal complement cascade (**Figure 3**) which was first approved for the treatment of paroxysmal nocturnal hemoglobinuria, a rare acquired hematological disorder. Atypical hemolytic uremic syndrome (aHUS) is an ultrarare disease caused by genetic abnormalities in proteins regularing the alternative complement pathway. Excessive complement activation leads to endothelial damage and thrombotic microangiopathy in the microvasculature of the kidneys but also other organs including the brain. Mortality is high and survivors tend to progress rapidly to end-stage renal disease, with up to 100% post-transplant recurrence rate.[91] Administration of Eculizumab induced complete disease remission in nearly all treated patients with remarkable recovery of renal function even after extended end-stage renal failure, turning a dismal disease into a permanently treatable condition.[92] Its highy selective mechanism of action and apparently excellent benefit-risk ratio makes Eculizumab an attractive target also for other complement-mediated diseases, including antibody-mediated allograft rejection and membranoproliferative glomerulonephritis.[92]

The majority of *AVPR2* mutations in X-linked Nephrogenic Diabetes Insipidus (NDI) and all *AQP2* mutations in autosomal recessive NDI result in normal protein that is retained within the endoplasmic reticulum. Agents that restore plasma routing are under investigation as potential treatments (**Figure 3**). Promising agents for X-linked NDI are cell-permeable *AVPR2* antagonists or agonists that *in vitro* rescue the intracellular retention of mutant *AVPR2*.[93-95] The therapeutic feasibility of these so-called pharmacologic "chaperones" has been tested *in vivo*. In individuals with missense *AVPR2* mutations, a non-peptide V1a receptor antagonist showed beneficial effects on urine volume and osmolality within hours of administration.[96] Whilst the long-term efficacy of this drug could not be tested since its clinical development was discontinued due to cytochrome P450 interaction, other pharmacologic chaperones in NDI await further *in vivo* testing. The chaperone approach may also become attractive for other genetic kidney diseases where point mutations lead to defective folding and cellular trafficking of otherwise intact membrane proteins (e.g. uromodulin-associated kidney diseases). Progress in this field will depend on the development of high-throughput compound screening compatible *in vitro* and *in vivo* model systems reproducing mutations in individual renal cell types.

4.3. Health policies

The global activities orchestrated by IRDiRC are aimed to stimulate scientific exploration and provision of competent clinical care to patients affected by rare diseases worldwide. While being made a public health priority, rare disease research is expected to have important repercussions on public health policies. Measures to translate research insights into clinical benefit include implementation of centers of competence for patients with rare disease with adequate diagnostic and therapeutic capabilities, systematic genetic counselling of affected families, early detection of relevant disorders by global or targeted public screening programs, and facilitated regulatory authority approval of novel orphan drugs.[97]

Also, insights from rare diseases research may be used to modify establish public health measures by identifying subsets of patients at particular risk for adverse effects. For instance, a study of children with idiopathic hypercalciuria identified mutations in the vitamin D metabolizing enzyme CYP24A1 as the underlying pathology.[98] Subsequently, mutations in this gene were also detected in patients who developed severe hypercalcemia following prophylactic bolus vitamin D administration, thereby identifying a subset of individuals intolerant to this generally advocated public health measure.

The role of patient organizations in supporting both clinical and basic research and closing the gap between increased mechanistic understanding and treatment for rare diseases is increasingly recognized.[99,100] Patients want to understand their disease. They are most often keen to team up with physicians and researchers to give ideas, share personal insights, provide biological samples, contact family members and promote and participate in clinical trials. Patient organizations foster these activities and provide support to the physician-researcher-patient-family community. Examples in the field of rare kidney disorders include associations for cystic kidney disorders, oxalosis and primary hyperoxaluria, cystinosis, Lowe syndrome, metabolic disorders, etc. Coalitions of patient organizations are now significant actors in national health policies. A coalition of patient organizations proved instrumental in working with the US Congress to pass the Orphan Drug Act in 1983, opening a new era for the development of orphan drugs. The foundation for the National Organisations of Rare Disorders (NORD), whose operations include funding research, lobbying for legislation to benefit the rare diseases community, spreading information, and helping individuals with rare diseases afford medication and treatment. In Europe, the foundation of Orphanet, a multi-lingual reference portal for information on rare diseases and orphan drugs, and EURORDIS, an alliance of more than 500 patient organisations active in the field of rare diseases, were major steps towards patient empowerment (**Table 3**). These organisations participate in the establishment of the European research agenda and in the work of the European Medicines Agency (EMA) and committees dealing with orphan drugs.

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Figure Legends:

Figure 1. Inherited kidney disorders linked to nephron segments.

Segmental distribution of rare inherited kidney diseases (cystic and developmental disorders are not included). Inset, structure of the glomerulus (PEC, parietal epithelial cells; BS, Bowman space; TP, tubular pole; Pod, podocyte; VP, vascular pole; *, capillary lumen).

Figure 2. **Application of -omics technologies in rare kidney diseases.**

Genomic studies and molecular profiling of kidney tissues, plain and exosome enriched urine, together with multiscalar bioinformatic analysis of critical disease pathways, will facilitate the development of mechanistic renal disease ontologies, diagnostic tests, biomarkers and novel therapeutic targets.

Figure 3. **Exemples of molecular targets in rare inherited kidney diseases.**

a. Cysteamine for nephropathic cystinosis. Cystinosis is caused by mutations or deletions in the *CTNS* gene that encodes cystinosin, a ubiquitous lysosomal proton-driven cystine transporter. Cystinosin acts as a H^+-driven lysosomal cystine transporter working in parallel with the vacuolar H^+-ATPase which acidifies the lysosome. The influx of H^+ in the lysosome drives the cystinosin-mediated transport of cystine from the lysosome to the cytosol. The cationic amino acid exporter PQLC2 plays an important role in cysteamine therapy of cystinosin. In healthy subjects, cystinosin and PQLC2 export cystine (the oxidized form of cysteine) and cationic amino acids, respectively, from the lysosomal lumen. Their activity is stimulated by the acidification of the lysosome lumen. In patients with cystinosis, the loss of function of cystinosin causes accumulation of cystine in the lysosomes. The drug cysteamine reduces the accumulation of cysteine accumulation by entering lysosomes and reacting with cystine to form a cysteamine-cysteine mixed disulfide, which resembles lysine. The mixed disulfide is then exported by PQLC2, thus depleting cystine from lysosomes and alleviating symptoms. *Modified from Jézégou A, Llinares E, Anne C, et al. Heptahelical protein PQLC2 is a lysosomal cationic amino acid exporter underlying the action of cysteamine in cystinosis therapy. Proc Natl Acad Sci U S A 2012; 109: E3434-43.*

b. Nephrogenic diabetes insipidus (NDI). In the principal cells lining the collecting ducts, stimulation of the vasopressin V2 receptor by the antiduretic hormone arginine vasopressin leads to an increase in cAMP, causing a protein kinase A-mediated phosphorylation of the water channels AQP2 and their subsequent insertion in the apical plasma membrane. The resulting increase in transcellular water permeability is essential to mediate urine concentration. The majority of mutations in *AVPR2* (X-linked NDI) and *AQP2* (autosomal recessive NDI) results in misfolded V2R and AQP2 mutants in the endoplasmic reticulum (ER, Class II mutations). Pharmacological chaperones can rescue such class II mutants from the ER. Cell-permeable V2R antagonists stabilize the structure of mutant V2R and allow them to exit the ER, mature in the Golgi, and subsequently translocate to the basolateral plasma membrane. At the membrane, vasopressin will displace the antagonist and will allow restoration of the cAMP cascade. V2R agonists function similarly and may also stimulate misfolded V2R in the ER without inducing maturation. Mutant AQP2 can be rescued from the ER by glycerol. *Modified from Wesche D, Deen PM, Knoers NV. Congenital nephrogenic diabetes insipidus: the current state of affairs. Pediatr Nephrol 2012; 27: 2183-204.*

c. Complement activation in atypical hemolytic uremic syndrome (aHUS). Patients with aHUS present a uncontrolled complement activation due to deficiency of natural complement regulatory factors (factors H, I and MCP), leading to membrane attack complex (C5b-9), activation of platelets, endothelial cell damage and systemic thrombotic microangiopathy. Eculizumab is a humanized monoclonal antibody that specifically inhibits the cleavage of the complement protein C5, thus blocking the activation of the complement system and the complement-mediated thrombotic microangiopathy in aHUS. *Modified from Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. Nat Rev Nephrol 2012; 8: 622-33.*

Table 1. Milestones in inherited kidney diseases.

Milestones in genetics :

* 1985: Mapping the first gene location for an inherited kidney disorder (autosomal dominant polycystic kidney disease, on chromosome 16) - *Reeders ST et al. Nature 1985; 317: 542-4*.

* 1990: First detection of a point mutation at a specific locus single-gene disorder, COL4A5 – *Barker DF et al. Science. 1990;248: 1224-7*.

* 1992: Molecular basis of nephrogenic diabetes insipidus - *Rosenthal W, et al. Nature. 1992 ;359:233-5*.

* 1994: Liddle syndrome due to activating mutation of the sodium channel ENaC - Shimkets RA et al. *Cell*. 1994;79:407-14.

* 1996: Molecular basis of Bartter and Gitelman syndromes - *Simon DB, et al. Nat Genet. 1996;12:24-30. Simon DB et al. Nat Genet. 1996;13:183-8*.

* 1996: Molecular basis for inherited kidney stone diseases - *Lloyd SE et al. Nature. 1996;379:445-9*.

* 1997: First nephronophthisis gene - *Hildebrandt F et al. Nat Genet. 1997;17:149-53*.

* 1998: Mutations in factor H cause atypical hemolytic uremic syndrome - *Warwicker P et al. Kidney Int. 1998;53:836–44*.

* 1998: Molecular basis of cystinosis - *Town M et al. Nat Genet. 1998;18:319-24*.

* 1999: Mutations in a paracellular protein (claudin-16) cause familial hypomagnesemia with hypercalciuria - *Simon DB et al. Science. 1999;285:103-6*.

* 2000: Podocin (NPHS2) is the major gene for steroid-resistant nephrotic syndrome - *Boute et al. Nat Genet 24: 349-354, 2000*.

* 2001: Mutations in different genes cause Bardet Biedl syndrome (digenic inheritance) - *Katsanis et al. Science 293: 2256-2259, 2001*.

* 2001: Mutations in WNK kinases alter the regulation of sodium, potassium and blood pressure - *Wilson FH, et al. Science. 2001;293:1107-12*.

*2002: Mutations in uromodulin (Tamm-Horsfall protein) cause familial juvenile hyperuricemic nephropathy, an autosomal dominant form of interstitial nephritis - *Hart TC, et al. J Med Genet. 2002;39:882-92*.

*2005: Mutations in a cation channel (TRPC6) causes glomerular disease - *Winn MP et al. Science. 2005;308:1801-4*.

*2010: First success of exome sequencing in rare renal disease:SDCCA8 in Senior Loken syndrome (retinal-renal ciliopathy) - *Otto et al, Nat Genet. 2010;42:840-50*.

*2011: Broadening spectrum of HNF1beta gene mutations - *Faguer S et al . Kidney Int. 2011;80:768-76*.

*2013: Description of MUC1 as the cause of medullary cystic kidney disease type 1 (MCKD1). The gene was missed by massively parallel sequencing, evidencing the need for refinement of analysis methods and assessment of clinical utility of whole exome sequencing for autosomal dominant heterogeneous conditions - *Kirby A et al. Nat Genet 45: 299-303, 2013.*

Milestones in treatment:

*1981: Oral cysteamine for cystinosis - *Yudkoff M et al. N Engl J Med. 1981;304:141-5*.

*2000: Enzyme replacement therapy for Fabry disease - *Schiffmann R, et al. Proc Natl Acad Sci U S A. 2000;97:365-70; Schiffmann R, et al. JAMA. 2001 Jun 6;285(21):2743-9*.

*2000: First *in-vitro evidence* that pharmacological chaperones can rescue cell-surface expression and function of misfolded vasopressin type-2 receptors in nephrogenic diabetes insipidus - *Morello et al, J Clin Invest. 2000; 105:887-95*.

*2008: Development of mTOR inhibitors for tuberous sclerosis - *Bissler JJ et al. N Engl J Med 2008;358:140-151*.

*2009: Eculizumab for atypical hemolytic uremic syndrome - *Nürnberger J, et al. N Engl J Med. 2009;360:542-4. Gruppo RA, Rother RP. N Engl J Med. 2009;360:544-6*.

*2012: First positive, randomized controlled trial for ADPKD - *Torres VE et al. N Engl J Med. 2012;367:2407-18*.

Note: The original references of the milestones are available in the Supplementary Material.

Table 2. List and classification of inherited kidney disorders.

	Trans mission	*Defective protein*	*Protein function*	*OMIM entry*
I. Genetic disorders of renal growth and structure				
Congenital abnormalities of the kidney and urinary tract				
Renal adysplasia	AR AR AR	Ret Pax2 Uroplakin-3α	Tyrosine kinase receptor Transcription factor Membrane protein	191830
Vesicoureteral reflux	AD	Tenascin-XB	extracellular matrix glycoprotein	
Renal coloboma syndrome	AD	Pax2	Transcription factor	120330
Renal cysts and diabetes syndrome	AD	HNF1ß	Transcription factor	137920
Branchio-oto-renal syndrome	AD AD	Eya1 Six5	Transcription factor Transcription factor	113650
Fraser syndrome	AR AR AR	Fras1 Grip1 Frem2	Extracellular matrix protein Receptor interacting protein Extracellular matrix protein	219000
Urofacial (Ochoa) syndrome	AR AR	Heparanase-2 (HPA2) Lrig2	Matrix enzyme Membrane protein	236730 615112
Hypoparathyroidism, deafness, renal disease syndrome	AD	GATA3	Transcription factor	146255
Kallmann syndrome	XL AR	Anosmin1 FGFR1	Adhesion-like protein, protease inhibitor Tyrosine kinase receptor	308700 147950
Split-hand/split-foot malformation	AD	(*dupl.10q24)*	-	246560
Townes-Brocks syndrome	AD	SALL1	Transcription factor	602218
Perlman syndrome (nephroblastomatosis, gigantism)	AR	DIS3L2	Ribonuclease	267000
Renal tubular dysgenesis	AR AR AR AR	Renin Angiotensinogen AT1 receptor ACE	Endopeptidase (angiotensinogenase) Secreted peptide G-protein coupled receptor Carboxypeptidase	267430

Ciliopathies				
Autosomal dominant polycystic kidney disease,	AD	Polycystin-1	Ciliary protein, regulates cilium length	173900
types 1 and 2	AD	polycystin-2	Ciliary protein, regulates cilium length	613095
Autosomal recessive polycystic kidney disease	AR	Fibrocystin	Receptor-like cilium/cytoskeleton protein (centrosome regulator)	263200
Medullary cystic kidney disease/	AD	MUC1	Surface glycoprotein with adhesive and anti-adhesive properties	174000
familial juvenile hyperuricemic nephropathy	AD	Uromodulin	Surface-bound and secreted glycoprotein	603860
	AD	Renin	Endopeptidase (angiotensinogenase)	613092
Nephronophthisis				
type 1 (= Joubert 4)	AR	Nephrocystin-1	Ciliary protein, involved in organiation of apical junctions	256100
type 2	AR	Inversin	Ciliary protein, associates with microtubules, inhibits WNT signaling	602088
type 3 (= Renal-hepatic-pancreatic S. 1)	AR	Nephrocystin-3	Ciliary protein, inhibits WNT signaling	604387
type 4	AR	Nephrocystin-4	Ciliary protein, invovlved in organiation of apical junctions	606966
type 5	AR	IQCB-1 (Nephrocystin-5)	Centrosome protein, Involved in ciliogenesis	609254
type 6 (= Joubert 5, Meckel 4)	AR	CEP290 (Nephrocystin-6)	Centrosome protein, involved in ciliogenesis	610188
type 7	AR	GLIS2	Transcription factor	611498
type 8 (= Joubert 7, Meckel 5)	AR	RPGRIP1L (Nephrocystin-8)	Centrosome protein, regulates TXA2 receptor signaling	611560
type 9	AR	NEK8 (Nephrocystin-9)	Ser/thr-protein kinase, targets proteins to cilia	613824
type 10 (= Senior-Loken 7)	AR	SDCCAG8 (Nephrocystin-10)	Centrosome-associated protein, may be involved in ciliogenesis	613615
type 11 (= (Joubert 6, Meckel 3)	AR	TMEM67 (Meckelin)	Ciliary protein, involved in centrosome migration	613550
type 12 (= Joubert 11)	AR	TTC21B	Ciliary protein, involved in retrograde ciliary transport	613820
type 13 (= Cranioectodermal dysplasia 4)	AR	WDR19	Ciliary protein, involved in retrograde ciliary transport	614377
type 14 (= Joubert 19)	AR	ZNF423	Centrosome protein, involved in DNA damage response	614844
type 15	AR	CEP164	Centrosome protein, involved in DNA damage response	614845
type 16	AR	ANKS6	Ciliary protein	615382
Joubert syndrome (only subtypes with renal phenotype)	AR	INPP5E	IP3 phosphatase	213300
type 1	AR	TMEM216	Ciliary protein, may be involved in ciliogenesis	608091
type 2	AR	NPHP1 (Nephrocystin-1)	Ciliary protein, involved in organiation of apical junctions	609583
type 4	AR	CEP290 (Nephrocystin-6)	Centrosome protein, involved in ciliogenesis	610188
type 5	AR	TMEM67 (Meckelin)	Ciliary protein, involved in centrosome migration	610688
type 6	AR	RPGRIP1L (Nephrocystin-8)	Centrosome protein, regulates TXA2 receptor signaling	611560
type 7	AR	CC2D2A	Ciliary protein, involved in ciliogenesis and SHH signaling	612285
type 9	XLR	OFD1	Centrosome protein, involved in ciliogenesis	300804
type 10	AR	TTC21B	Ciliary protein, involved in retrograde ciliary transport	613820

type 11	AR	TMEM237	Ciliary protein, involved in ciliogenesis	614424
type 14	AR	CEP41	Centrosome protein, required during ciliogenesis	614464
type 15	AR	TMEM138	Multi-pass transmembrane protein required for ciliogenesis	614465
type 16	AR	TCTN3	Membrane protein, required for ciliogenesis and SHH signaling	614815
type 18	AR	ZNF423	Centrosome protein, involved in DNA damage response	614844
type 19	AR	TMEM231	Ciliary protein, required for ciliogenesis and SHH signaling	
type 20				
Meckel-Gruber syndrome				
type 1	AR	MKS1	Ciliary protein, regulates cilia structure and function	209900
type 2	AR	TMEM216	Ciliary protein, may be involved in ciliogenesis)	603194
type 3	AR	TMEM67 (Meckelin)	Ciliary protein, involved in centrosome migration	607361
type 4	AR	CEP290 (Nephrocystin-6)	Centrosome protein, involved in ciliogenesis	611134
Short rib-polydactyly syndrome (Jeune S.)				
type 1	AR	*unknown*	-	263530
type 2	AR	NEK1	Centrosomal Ser/Thr protein kinase, involved in ciliogenesis	263520
type 3	AR	Dynein	Ciliary protein, involved in retrograde ciliary transport	263510
type 4	AR	*unknown*	-	269860
type 5	AR	WDR35	Ciliary protein, involved in retrograde ciliary transport	614091
type 6	AR	WDR60	Cilium base protein, involved in ciliogenesis	615503
Bardet-Biedl syndrome				
type 1	AR	BBS1	BBSome complex protein, required for ciliogenesis	209900
type 2	AR	BBS2	BBSome complex protein, required for ciliogenesis	
type 3	AR	ARL6	Cilium base protein, targets BBSome to plasma membrane	
type 4	AR	BBS4	BBSome complex protein, required for ciliogenesis	
type 5	AR	BBS5	BBSome complex protein, required for ciliogenesis	
type 6	AR	MKKS	Chaperone, may assist folding of BBSome proteins	
type 7	AR	BBS7	BBSome complex protein, required for ciliogenesis	
type 8	AR	TTC8	BBSome complex protein, required for ciliogenesis	
type 9	AR	PTHB1	BBSome complex protein, required for ciliogenesis	
type 10	AR	BBS10	Chaperone, affects folding/ stability of ciliary/basal body proteins	
type 11	AR	TRIM32	E3 ubiquitin ligase activity	
type 12	AR	BBS12	Chaperone, assists folding of BBSome proteins	
type 13	AR	MKS1	Ciliary protein, regulates cilia structure and function	
type 14	AR	CEP290	Centrosome protein, involved in ciliogenesis	
type 15	AR	Human fritz (C2orf86)	Controls ciliogenesis by regulating septin cytoskeleton	

Alström syndrome	AR	ALMS1	Centrosome protein, required for cilia formation/maintenance	203800
Cranioectodermal dysplasia, types 1-4 (Sensenbrenner syndrome)	AR	IFT122 WDR35 IFT43 WDR19	Ciliary protein, involved in retrograde ciliary transport Ciliary protein, involved in retrograde ciliary transport Ciliary protein, involved in retrograde ciliary transport Ciliary protein, involved in retrograde ciliary transport	218330 613610 614099 614378
Oral-facial-digital syndrome type 1	XLD	OFD1	Centrosome protein, involved in ciliogenesis	311200
Renal-hepatic-pancreatic dysplasia (Ivemark syndrome)	AR	Nephrocystin-3 NEK8 (nephrocystin-9)	Ciliary protein, inhibits WNT signaling Ser/Thr protein kinase, may target proteins to cilia	208540 615415
II. Genetic disorders of renal function				
Glomerular diseases				
Autosomal recessive SRNS	AR	Nephrin podocin PLCE1 MYO1E PTPRO Diacyl glyerol kinase-ε ARHGDIA ARHGAP24	Podocyte adhesion receptor, component of slit diaphragm Podocyte membrane protein, links slit diaphragm to cytoskeleton Phospholipase, regulates PKC pathway and small GTPases Cytoplasmic protein, regulates actin cytoskeleton functions Receptor-type tyrosine phosphatase Enzyme involved in cell signaling, activates PKC pathway Cytoplasmic protein, involved in Rho protein signaling Rho GTPase-activating protein	256300 600995 610725 614196 614455 601440 615244
Autosomal dominant SRNS	AD	WT1 Inverted formin-2 (INF2) α-actinin-4 (ACTN4) TRPC6	Transcription factor Cytoplasmic protein, severs actin filaments F-actin cross-linking cytoplasmic protein Receptor-activated calcium channel	256370 613237 603278 603965
Denys-Drash syndrome, Frasier syndrome	AD	WT1	Transcription factor	194080 136680
WAGR syndrome	AD	WT1 / Pax6	Transcription factors	194072
Pierson syndrome	AR	Laminin-ß2	Extracellular matrix glycoprotein	609049
Nail-Patella syndrome	AD	LMX1B	Transcription factor	161200
Schimke immuno-osseous dystrophy	AR	SMARCAL1	Annealing helicase, catalyzes rewinding of unwound DNA	
Mitochondrial disorders with SRNS: Primary CoQ10 deficiency, types 1 and 6	AR	 COQ2 COQ6 ADCK4	 Enzyme involved in COQ10 biosynthesis Enzyme involved in COQ10 biosynthesis Mitochondrial protein involved in CoQ10 biosynthesis	 607426 614650
Fabry disease	XL	alpha-galactosidase A	Lysosomal enzyme, catalyzes galactosyl-glycolipid moieties	301500

Alport syndrome	XL AR	Collagen IV α-5, Collagen IV α-4, Collagen IV α-3	α5-chain of type IV collagen α4-chain of type IV collagen α3-chain of type IV collagen	301050 203780
Benign familial hematuria (thin basement membane nephropathy)	AD	Collagen IV α-3	α3-chain of type IV collagen	141200
Fechtner syndrome (Alport syndrome with macrothrombocytopenia)	AD	MYH9	Non-muscle myosin, inolved in cell shape and movement	153640
Alport syndrome with leiomyomatosis	XL	Collagen IV alpha-5 + Collagen IV α-6	α5- and α6-chains of type IV collagen	308940
Familial amyloidosis	AD	Fibrinogen A-α lysozyme APOA1 ß2-microglobulin	Secreted protein Secreted enzyme Secreted lipoprotein Secreted protein	105200
Renal tubular diseases and metabolic diseases				
Renal glucosuria	AR/AD	SLC5A2	Sodium/glucose cotransporter	233100
Dicarboylic aminoaciduria	AR	SLC1A1	Glutamate transporter	222730
Lysinuric protein intolerance	AR	SLC7A7	Cationic Amino Acid Transporter	222700
Proximal renal tubular acidosis	AR	SLC4A4	Sodium bicarbonate cotransporter	604278
Distal renal tubular acidosis	AD	SLC4A1	Inorganic anion transmembrane transport protein	179800
Renal tubular acidosis with osteopetrosis	AR	Carbonic anhydrase II	Enzyme involved in bicarbonate transport	611492
Hypophosphatemic rickets	XL	PHEX	Endopeptidase, degrades FGF23	307800
	AD	FGF23	Osteocyte hormone, inhibits tubular phosphate reabsorption	193100
	AR AR	ENPP1 DMP1	Pyrophosphatase, regulates mineralization Osteoblast transcriptional activator/osteocyte matrix regulator	613312
Nephropathic cystinosis		Cystinosin (CTNS)	Lysosomal membrane cystine transporter	606272
Primary Fanconi syndrome types 1 and 2	AD AR	15q15.3 SLC34A1(NaPi3)	Affected gene(s) unknown Sodium/phosphate cotransporter	134600 182309
Fanconi-Bickel syndrome (hepatorenal glycogenosis)	AR	SLC2A2(GLUT2)	Facilitated glucose transporter	227810
Dent disease, type 1 Dent disease, type 2 Lowe oculocrebrorenal syndrome	XL XL XL	ClC-5 Inositol polyphosphate 5-phosphatase (OCRL1)	Chloride-proton exchanger 5-phosphatase, regulates early endosomes	300009 300535 309000
Hereditary renal hypouricemia	AR	URAT1 (SLC22A12)	Urate transporter	220150
Bartter syndrome types 1-4	AR	SLC12A1	Sodium-potassium-chloride cotransporter	601678

		KCNJ1 CLCNKB CLNCKA BSND (Barttin)	Potassium channel Chloride channel Chloride channel ß-subunit of CLCNKA and CLCNKB chloride channels	241200 607364 602522
Familial juvenile hyperuricemic nephropathy Medullary cystic kidney disease type 2	AD	Uromodulin (Tamm-Horsfall protein)	Secretory protein	162000 603860
Familial hypocalciuric hypercalcemia type 1 Neonatal severe hyperparathyroidism Autosomal dominant hypocalcemia (incl. with Bartter syndrome	AD AR AD	CASR CASR CASR	Calcium-sensing receptor (loss of function) Calcium-sensing receptor (loss of function) Calcium-sensing receptor (gain of function)	145980 239200 601198
Gitelman syndrome	AR	SLC12A3	Thiazide-sensitive sodium/chloride cotransporter	263800
Hypomagnesemia (intestinal, type 1) with secondary hypocalcemia Hypomagnesemia (renal, type 2) Hypomagnesemia (renal, type 3) Hypomagnesemia (renal, type 4) Hypomagnesemia (renal, type 5) with hypercalcinuria, nephrocalcinosis and ocular involvement Hypomagnesemia (renal, type 6)	AR AD AR AR AR AD	TRPM6 FXYD2 Claudin 16 EGF Claudin 19 Cyclin-M2	Magnesium channel Gamma subunit of sodium-potassium-ATPase Paracellular protein, component of tight junctions Epidermal growth factor Paracellular protein, component of tight junctions Membrane protein of unknown function	602014 154020 248250 611718 248190 613882
Liddle syndrome	AD	SCNN1G, SCNN1B	**γ**-subunit of amiloride-sensitive sodium channel (gain of function) ß-subunit of amiloride-sensitive sodium channel (gain of function)	177200
Pseudohypoaldosteronism type 1	AR	SCNN1A SCNN1G SCNN1B	α-subunit of amiloride-sensitive sodium channel **γ**-subunit of amiloride-sensitive sodium channel ß-subunit of amiloride-sensitive sodium channel	264350
Pseudohypoaldosteronism type 2 (Gordon syndrome)	AD	WNK1 WNK4 KLHL3 Cullin-3	Ser/thr kinase modulating Na- and K-coupled Cl transporters Ser/thr kinase modulating Na- and K-coupled Cl transporters Structural protein mediating ubiquitination of SLC12A3 Component of ubiquitin E3 ligase complex	145260
SeSAME syndrome (EAST syndrome)	AR	KCNJ10	Potassium channel	612780
Distal renal tubular acidosis Distal renal tubular acidosis, with hemolytic anemia Distal renal tubular acidosis, with progressive nerve deafness	AR AR AR	ATP6V0A4 SLC4A1 ATP6V1B1	Subunit of the vacuolar proton ATPase Anion exchanger (Erythroid band 3) Subunit of the vacuolar proton ATPase	602722 611590 267300

Nephrogenic diabetes insipidus type 1	XL	Vasopressin V2 receptor	G-protein coupled receptor for arginine vasopressin (loss of function)	304800
Nephrogenic syndrome of inappropriate antidiuresis	XL	Vasopressin V2 receptor	G-protein coupled receptor for arginine vasopressin (gain of function)	300539
Nephrogenic diabetes insipidus type 2	AD/AR	Aquaporin 2	Water channel	125800
Nephrolithiasis				
Cystinuria	AD AR	SLC3A1 SLC7A9	Activator of cystine transporter SLC7A9 Cystine transporter	220100
Dent disease type 1 Dent disease type 2 Lowe oculocerebrorenal syndrome	XL XL XL	ClC-5 Inositol polyphosphate 5-phosphatase (OCRL1)	Chloride-proton exchanger 5-phosphatase, regulates early endosomes	300009 300535 309000
Primary hyperoxaluria type I	AR	Alanine-glyoxylate aminotransferase	Vitamin B6-dependent peroxisomal enzyme	259900
Primary hyperoxaluria type II	AR	Glyoxylate reductase/ hydroxypyruvate reductase	Peroxisomal enzyme	260000
Primary hyperoxaluria type III	AR	4-hydroxy-2-oxoglutarate aldolase (HOGA1)	Mitochondrial enzyme (hydroxyproline metabolic pathway)	613616
Adenine-phosphoribosyl-transferase deficiency	AR	Adenine phosphoribosyl-transferase (APRT)	Cytoplasmic enzyme forming AMP from adenine	614723
Xanthinuria type 1	AR	Xanthine dehydrogenase	Key enzye in purine degradation	278300

Table 3. Examples of European and international networks focusing on rare inherited kidney diseases.

- EPIRARE: European Platform for Rare Disease Registries (www.epirare.eu)
- PARENT: Patient Registries Initiative (www.patientregistries.eu)
- RD-CONNECT: An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research (www.rd-connect.eu)
- IRDiRC: International Rare Diseases Research Consortium (www.irdic.org)
- EURenOmics: EURenOmics integrates a large number of registries and biobanks with detailed phenotype information and biomaterials from cumulatively more than 13,000 patients (www.eurenomics.eu)
- ERA-EDTA WGIKD: Working Group on Inherited Kidney Diseases (http://www.era-edta.org/wgikd/ERA-EDTA_working_group_on_Inherited_kidney_disorders.htm)
- NORD: National Organization for Rare Disorders (www.rarediseases.org)
- ORPHANET: The portal for rare diseases and orphan drugs (www.orpha.net)
- EURORDIS: The European Organization for Rare Diseases (www.eurordis.org)
- EMA and orphan designation: European Medicines Agency (www.ema.europa.eu)

Rare Inherited Kidney Diseases: Challenges, Opportunities and Perspectives

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on behalf of the Board of the Working Group for Inherited Kidney Diseases of ERA-EDTA

Supplementary Material

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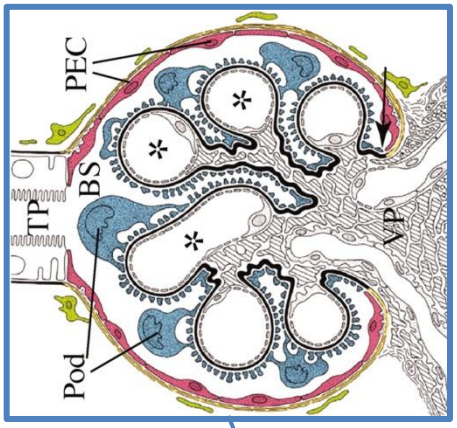
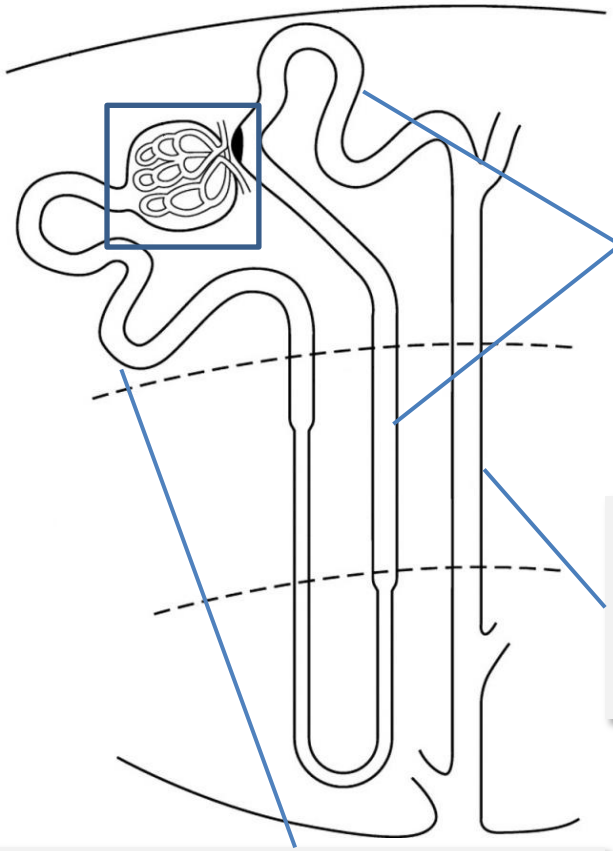
Figures 1 to 3

Figure 1: Inherited kidney disorders linked to nephron segments.



Glomerular diseases
- Congenital steroid-resistant nephrotic syndrome (SRNS)
- Denys-Drash syndrome, Frasier syndrome
- Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation (WAGR) syndrome
- Pierson syndrome
- Nail-Patella syndrome
- Schimke immuno-osseous dystrophy
- Mitochondrial disorders with SRNS
- Fabry disease
- Alport syndrome (AS)
- Benign familial hematuria (thin basement membrane)
- Fechtner syndrome (AS with macrothrombocytopenia)
- AS with leiomyomatosis
- Familial amyloidosis



Thick ascending limb of Henle's loop and distal convoluted tubule
- Bartter syndrome types 1–4
- Familial hypocalciuric hypercalcemia
- Neonatal severe hyperparathyroidism
- Autosomal dominant hypocalcemia
- Gitelman syndrome
- Pseudohypoaldosteronism type 2 (Gordon syndrome)
- SeSAME syndrome (EAST syndrome)
- Hypomagnesemia types 1-6
- Familial juvenile hyperuricemic nephropathy

Collecting duct
- Liddle syndrome
- Distal renal tubular acidosis
- Pseudohypoaldosteronism type 1
- Nephrogenic diabetes insipidus types 1 and 2
- Nephrogenic syndrome of Inappropriate antidiuresis

Proximal tubule
- Renal glucosuria
- Dicarboylic aminoaciduria
- Lysinuric protein intolerance
- Proximal renal tubular acidosis
- Hypophosphatemic rickets
- Nephropathic cystinosis
- Primary renal Fanconi syndrome types 1 and 2
- Fanconi-Bickel syndrome (Hepatorenal glycogenosis)
- Lowe syndrome
- Dent disease types 1 and 2
- Hereditary renal hypouricemia
- Cystinuria, types 1-3

Figure 2: Application of -omics technologies in rare kidney diseases.

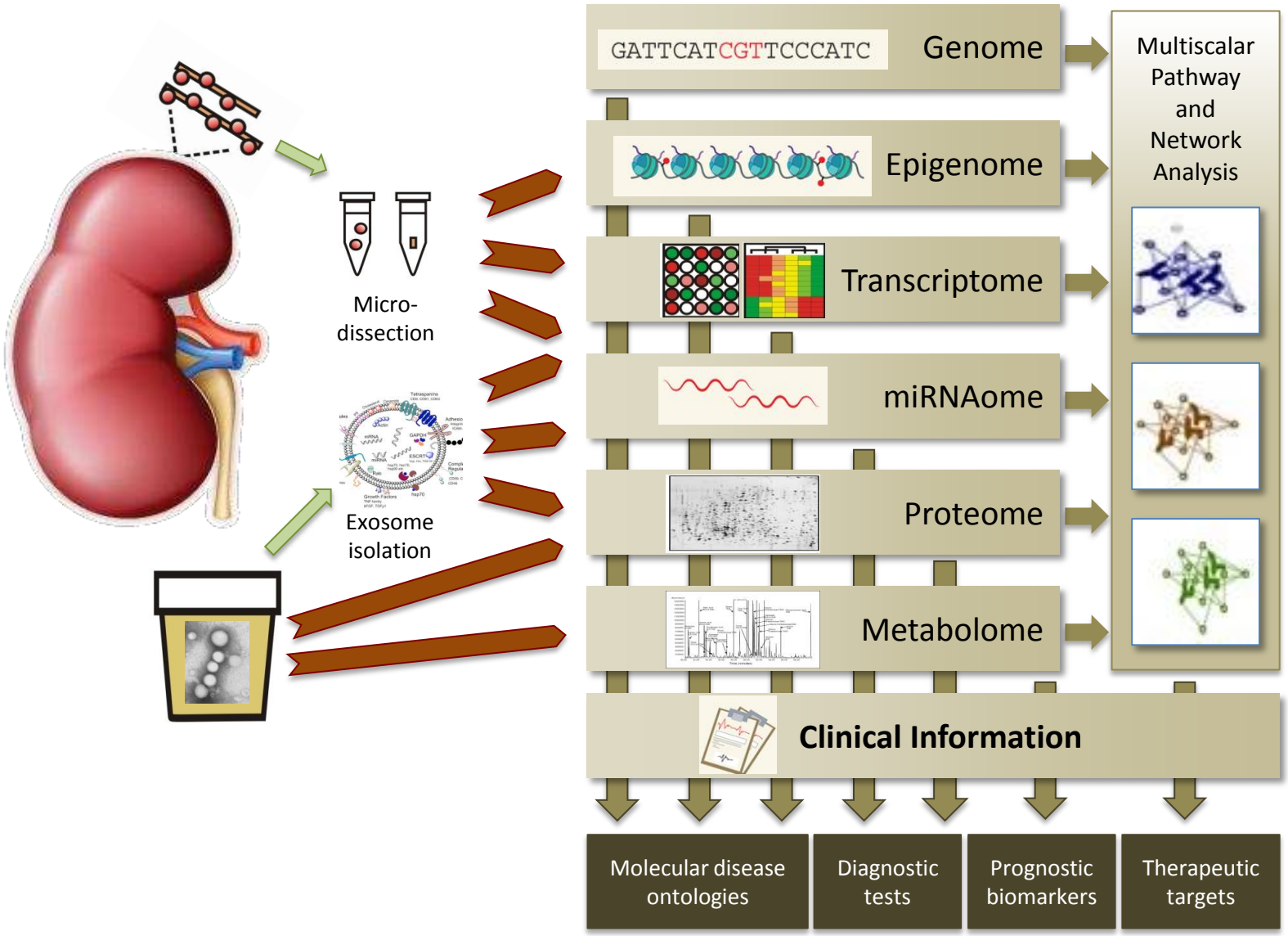
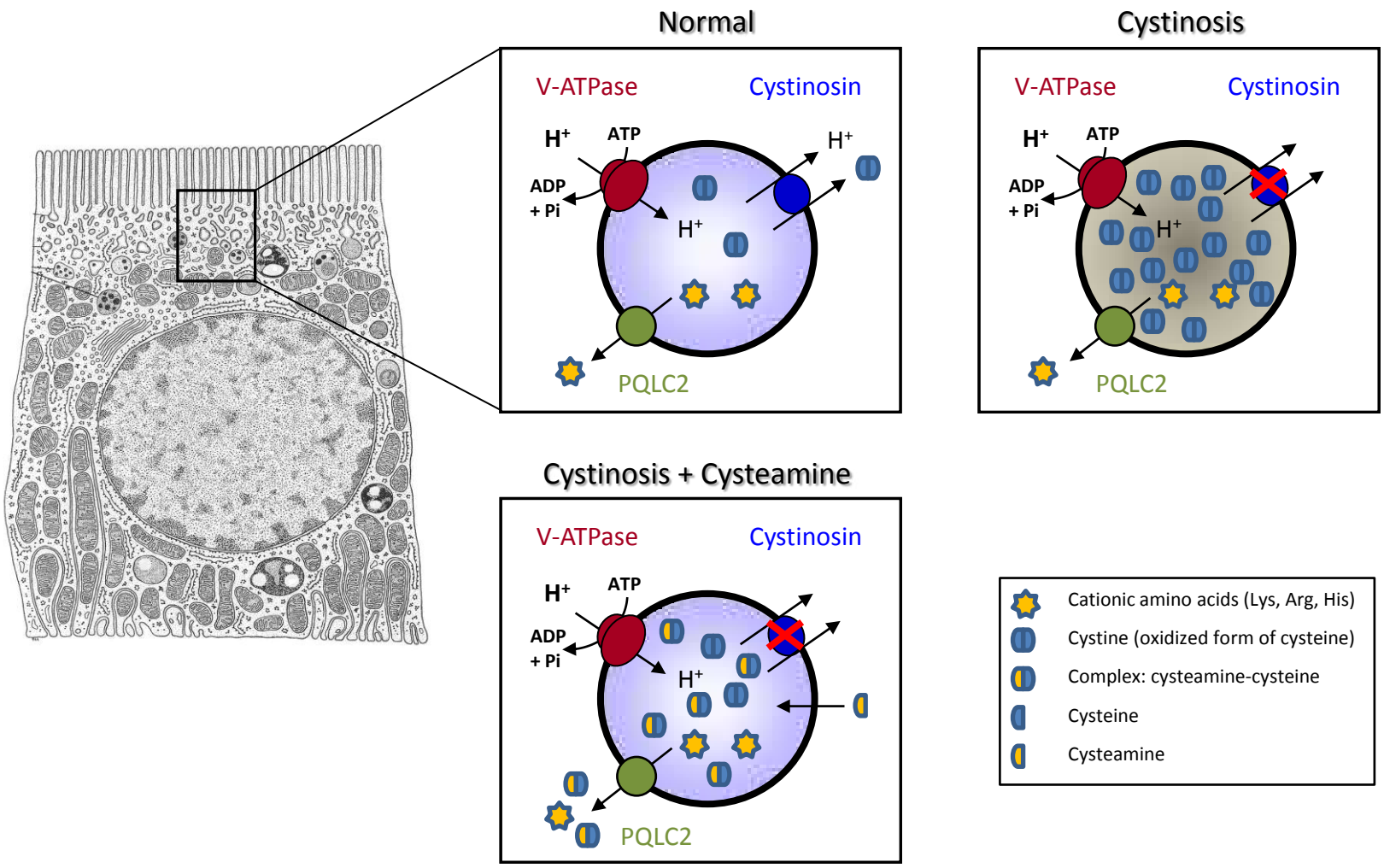


Figure 3: Exemples of molecular targets in rare kidney disorders.

a. Cysteamine for nephropathic cystinosis



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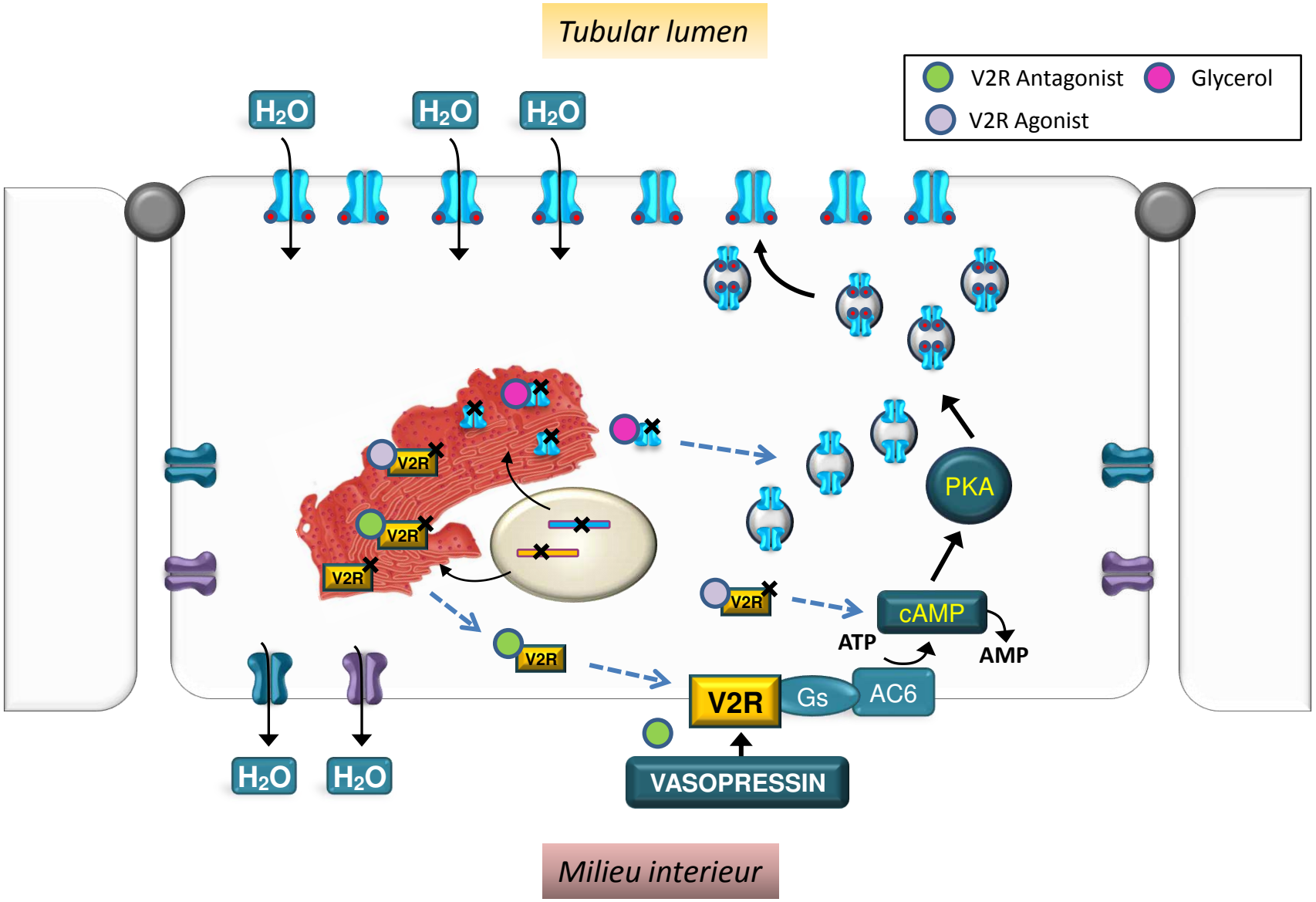
b. Nephrogenic diabetes insipidus



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c. Complement activation in atypical hemolytic uremic syndrome